PATENT SPECIFICATION

928,007

NO DRAWINGS

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Date of Application and filing Complete Specification: May 29, 1961.

No. 19341/61.

Application made in Germany (No. B58113 IVb/12p) on June 3, 1960.

Complete Specification Published: June 6, 1963.

Index at acceptance:—Classes 2(3), C1E4K(1:4:6), C1E5K(1:4:6), C2B(18:20:33:34), C3A12(A4A:A4B:B1:C5), C3A13B3, C3A13C(1C:2C:3C:6C:7:9:10F:10G:10H), CB4(A4:B:H:J:M); and 41, B2C.

International Classification:—C07c, d. (B01k).

COMPLETE SPECIFICATION

Substituted Pyrrolidines

ERRATA

SPECIFICATION NO. 928,007

Page 1, Classification:- *for* "C07c,d. (B01k)." *read* "C07c,d(B01k)."

Page 2, line 39, *for* "formula II" *read* "formula III"

Page 2, line 64, *for* "meetings" *read* "meanings"

Page 4, line 103, *for* "contrasting" *read* "contracting"

Page 5, line 96, *insert* a colon *after* "pt"

Page 5, line 117, *insert* a colon *after* "tartrate"

Page 7, line 4, *for* "benzoyloxyphenyl" *read* "benzyloxyphenyl"

Page 7, line 15, Page 8, lines 29 and 120 and Page 9, line 75, *insert* a full-stop *after* "pt"

Page 7, line 19, *insert* a hyphen *after* "methoxyphenyl)"

Page 8, line 46, *for* "-130C." *read* "130°C."

Page 8, line 66, *for* "183-195°C." *read* "183-185°C."

Page 9, line 22, *for* "salicyclic" *read* "salycylic"

Page 12, lines 10 and 62, and Page 11, line 6, *for* "wherein" *read* "where"

THE PATENT OFFICE,
16th July 1963

DS 75345/1(10)/R.109 200 7/63 PL

gen atoms or alkyl, alkoxy, hydroxy or methylenedioxy groups, at least one of the symbols Z representing a phenyl group substituted with at least one alkoxy, hydroxy or methylenedioxy group, and their acid addition salts.

The new compounds may be produced in 100°C.) are advantageous but the hydrogen pressure is preferably below that at which hydrogenation of the nucleus normally takes place (advantageously at 5—20 atmospheres excess pressure). The reductions can also be carried out with Adkins catalysts (for example copper-chromium oxide), but this method

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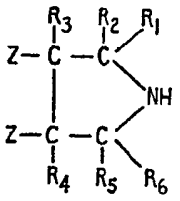
COMPLETE SPECIFICATION

Substituted Pyrrolidines

We, ERNST BOEHRINGER, ILSE LIEBRECHT, JULIUS LIEBRECHT, WALTER MAYER-LIST, WILHELM DIRIK BOEHRINGER and HERMANN ALBERT BOEHRINGER all of German nationality trading in partnership as C. H. BOEHRINGER SOHN, of Ingelheim am Rhein, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention concerns new 3-phenyl - pyrrolidines and their salts and a process for their production.

According to the present invention we provide phenyl - pyrrolidines of the general formula

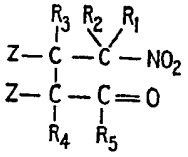


I

where R_1, R_2, R_3, R_4, R_5 and R_6, which may be the same or different, are hydrogen atoms or alkyl groups containing 1 to 6 carbon atoms, at least one of R_1, R_2, R_5 and R_6 representing a hydrogen atom and the symbols Z, which may have the same or different meanings represent hydrogen atoms or phenyl or endomethylenecycloalkyl groups, if desired substituted with one or more halogen atoms or alkyl, alkoxy, hydroxy or methylenedioxy groups, at least one of the symbols Z representing a phenyl group substituted with at least one alkoxy, hydroxy or methylenedioxy group, and their acid addition salts.

The new compounds may be produced in any convenient way; the following methods have proved to be particularly advantageous.

(1) Reduction of 1,4 - nitrocarbonyl compounds of the formula



II

wherein R_1, R_2, R_3, R_4, R_5 and Z have the above-stated meanings. This process leads only to those compounds of general formula I in which R_6 is hydrogen. When R_5 in general formula II is hydrogen it is advantageous to use not the free aldehyde but an acetal thereof.

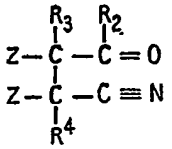
The reduction can take place for example, chemically or electrolytically. Thus, for example, catalytic hydrogenation is possible, preferably using Raney or noble metal catalysts. Where Raney catalyst is used (preferably Raney nickel or Raney cobalt) the hydrogenation preferably takes place at 50°—150°C., advantageously at 80°—100°C. and at hydrogen pressures above 50 atmospheres excess pressure advantageously at 80—150 atmospheres excess pressure. On the other hand, if a noble metal catalyst is used, for example, palladium on a support (charcoal, $BaSO_4$,) platinum with or without a support, rhodium catalysts containing rhodium oxide or mixed catalysts containing the noble metals named, elevated temperatures (usefully 50—100°C.) are advantageous but the hydrogen pressure is preferably below that at which hydrogenation of the nucleus normally takes place (advantageously at 5—20 atmospheres excess pressure). The reductions can also be carried out with Adkins catalysts (for example copper-chromium oxide), but this method

offers no advantages over reductions with Raney catalysts because temperatures above 180°C. and pressures above 150 atmospheres excess pressure are necessary for a complete reaction. Under these conditions increased resinification takes place. In the catalytic hydrogenation, inert solvents such as lower alcohols e.g. methanol, ethanol, isopropanol, glycol mono - ethylether, etc. or ethers e.g. dioxan, etc. can advantageously be used, advantageously giving dilutions of 1:5 (parts by vol) since more concentrated solutions favour side reactions. Where Adkins catalysts are used, however, alcohols are not suitable as solvents, since they are also reduced in the reaction. In this case ethers, such as dioxan, are preferred as inert solvents.

In the electrolytic reduction it is advantageous to use lead cathodes and to work at a current density of at least 0.1 amps/cm². According to a preferred method 50% sulphuric acid is used as electrolyte and lower alcohols e.g. methanol, are used as solvent.

The 1,4 - nitrocarbonyl compounds used as starting products can be produced for example, by reaction of benzylidene ketones with nitroalkyls. Examples of starting material for this process include, for example, 1 - nitro-2 - (*p* - methoxyphenyl) - pentanone - (4) and 1 - nitro - 2 - (*m,p* - dimethoxyphenyl)-pentanone - (4).

(2) Reduction of 1 - cyano - 3 - oxo compounds of the formula

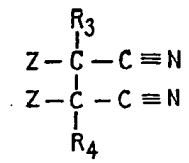


III

wherein R_2, R_3, R_4 and Z have the above-stated meanings. This method may be used to prepare directly only those compounds of formula I in which R_1, R_5 and R_6 are hydrogen atoms. Where R_2 in formula II is hydrogen, it is advantageous not to use the free aldehyde but an acetal thereof. The reduction can be carried out chemically or electrolytically as in method 1. The cyano-ketones used as starting material may be obtained, for example, by reacting benzyl cyanides with halogenoketones in the presence of sodamide, by amino group-exchange in amino-ketones (Mannich bases) using potassium cyanide or by reacting hydrocyanic acid with alkylethylene ketones, if desired with the aid of acetone cyanhydrin.

The cyano - aldehydes and their derivatives used as starting materials may be obtained by reacting benzyl cyanides with halogeno-aldehyde acetals in the presence of sodamide. Examples of starting materials which may be used include β - (*p* - methoxy phenyl)-laevulinic acid nitrile and α-(*m,p*-methylene-dioxy - phenyl) - β - phenyl - laevulinic acid nitrile.

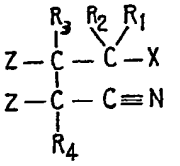
(3) Reduction of succinodinitriles of the general formula



IV

where R_3, R_4 and Z have the above meetings. This method produces compounds of general formula I in which R_1, R_2, R_5 and R_6 are all hydrogen. The reduction may be carried out chemically or electrolytically as in method 1. The dinitriles serving as starting materials can be obtained by the processes which are normally used in the production of succinic acid dinitriles. Starting materials for process 3, include, for example, 2 - (*p* methoxyphenyl) - 3 - ethyl - succinodinitrile and 2-(*p* - methoxyphenyl) - 3 - (*p* - methoxy - *m*-methylphenyl) - succinodinitrile.

(4) Reduction of 1 - nitro or 1 - amino - 4-nitriles of the general formula



V

wherein X signifies an amino or nitro group and R_1, R_2, R_3, R_4 and Z have the above-stated meanings. This process leads only to compounds of formula I in which R_5 and R_6 are hydrogen.

The reduction can be carried out chemically or electrolytically, as in process 1. Nitronitriles serving as starting compounds can be produced, for example, by addition of nitroalkyls to substituted acrylonitriles.

The 1,4 - amino - nitriles serving as starting compounds can be obtained, for example, by reduction of the corresponding nitronitrile with metal and acid, e.g. zinc and hydrochloric acid, or by reaction of benzylcyanides with β - halogenalkylamines or their hydrochlorides in the presence of sodamide. The amino groups of the β - halogen alkylamines are advantageously temporarily protected by easily removable groups e.g. by the benzyl residue.

Starting compounds for this process include for example

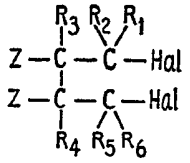
1 - cyano - 1 - (*m,p* - dimethoxyphenyl)-2 - (*m* - methoxy - *p* - benzyloxy - phenyl)-3 - nitro - propane,

1 - cyano - 1 - (*m* - methyl - *p* - methoxyphenyl) - 2 - (*m,p* - methylendioxyphenyl)-3 - nitro - pentane,

1 - cyano - 1 - (*p* - methoxyphenyl) - 3-(dibenzylamino) - propane,

1 - cyano - 1 - (*m,p* - dimethoxyphenyl)-3 - (dibenzylamino) - propane.

(5) Reaction of butylene 1,4 - dihalides of the general formula

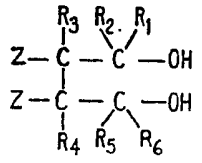


VI

wherein R_1, R_2, R_3, R_4, R_5, R_6 and Z have the above-stated meaning and Hal is a chlorine, bromine or iodine atom with ammonia or benzylamine and, if the reaction takes place with benzylamine, reductive removal of the benzyl residue after ring closure.

The reaction is preferably effected in alcohol solution at temperatures between 60 and 120°C. Lower alcohols such as ethanol, isopropanol, glycol, ether solvents, for example glycolmonoethylether or dioxan and other inert solvents, for example hydrocarbon solvents, e.g. benzene, may be used as solvent medium. Using ammonia as base it is advantageous to carry out the reaction in an autoclave. The ratio of dichloride to base for optimal yield should be at least 1:2 and advantageously not more than 1:3.5. It can be of particular advantage to carry out the reaction in presence of a hydrogen halide binding agent for example K_2CO_3, triethylamine etc. The ratio of dichloride to ammonia or benzylamine is then advantageously between 1:1 and 1:1.5.

(6) Reaction of butylene - 1,4 - diols of the general formula

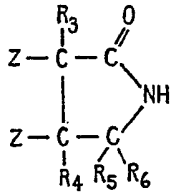


VII

wherein R_1, R_2, R_3, R_4, R_5 and R_6 have the above-stated meaning, their diesters, with ammonia or benzylamine. If the reaction is effected with benzylamine the benzyl residue is subsequently removed, e.g. by hydrogenolysis.

The reaction is preferably effected in alcohol solution at temperatures between 60 and 120°C. Lower alcohols such as ethanol, isopropanol, glycol, ether solvents, for example, glycolmonoethylether or dioxan and other inert solvents, for example hydrocarbon solvents, e.g. benzene, may be used as solvent medium.

(7) Reduction of α - pyrrolidones of the general formula



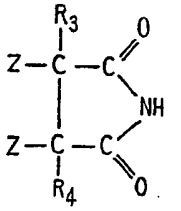
VIII

in which R_3, R_4, R_5, R_6 and Z have the above-stated meanings by metal hydride reducing agents such as $LiAlH_4$ or boron hydrides or electrolytically. It is also possible to reduce these compounds with an Adkins catalyst (e.g. copper-chromium) at a hydrogen pressure of 150 atmospheres excess pressure and at temperature of above 150°C., advantageously at 200—250 atmospheres excess pressure and 180—200°C. The reaction is advantageously effected in an inert solvent medium; dioxan is particularly suitable.

This process leads only to compounds of formula I in which R_1 and R_2 are hydrogen.

The production of the α - pyrrolidones used as starting substances may take place according to conventional processes.

(8) Reaction of succinic acid imides of the general formula

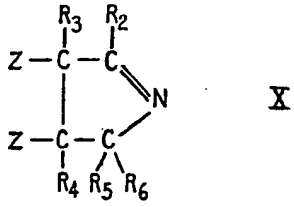


IX

wherein Z, R_3 and R_4 have the above-stated meanings, by metal hydride reducing agents e.g. $LiAlH_4$ or boron hydrides or electrolytically. It is also possible to reduce these compounds with Adkins catalysts (e.g. copper-chromium) at a hydrogen pressure of 150 atmospheres excess pressure and at a temperature of above 150°C., advantageously at

200—250 atmospheres excess pressure and 180—200°C. It is advantageous to use an inert solvent medium; dioxan is particularly suitable. The production of the succinic acid imides, used as starting substances may take place by conventional processes. This process leads only to compounds of formula I in which R_1, R_2, R_3, R_6 are hydrogen.

(9) Catalytic reduction of pyrrolines of the general formula



X

wherein R_2, R_3, R_4, R_5, R_6 and Z have the above-stated meanings.

The pyrrolines used as starting substances may be produced by conventional processes. Thus, for example, it is possible to reduce the nitroketones used in process 1, to aminoketones by means of zinc/hydrochloric acid, these aminoketones, after splitting off of water, forming pyrrolines which can be reduced to pyrrolidines of general formula I. It is also possible to react 1,4-cyano - halides with alkyl magnesium halides under the conditions of a Grignard reaction. The iminomagnesium halides formed as non-isolated intermediate products split off magnesium halide on heating and are converted into the corresponding pyrrolines.

This process leads only to compounds of formula I, in which R_1 is hydrogen.

(10) Subsequent halogenation of pyrrolidines of general formula I, produced according to one of the processes 1—9, in the phenyl group. The point of attachment of the halogen is determined by the substituents already present. Glacial acetic acid and lower halogenated hydrocarbons, for example chloroform and carbon tetrachloride, are preferred solvents. The reaction is preferably effected at room temperature.

In the production of compounds of general formula I, in which Z signifies a phenyl group with one or more free hydroxy groups it is advantageous to start from compounds in which the hydroxy group is protected, for example by an acyl, alkyl or aralkyl residue which can be split off. The splitting off of the protecting groups may then take place by conventional process. Thus, for example, alkoxy groups may be converted into hydroxy groups by reaction with an ether-splitting agent, for example hydrogen bromide.

The pyrrolidines of general formula I are generally produced in the form of mixtures of stereoisomeric forms or racemates. These mixtures can be separated into the cis- and trans-form or the optically active antipodes. By suitable choice of the reaction conditions it is possible however to arrive at purely stereoisomeric forms or to control the ratio of the isomers in mixtures. Cis-trans-mixtures can advantageously be separated by fractional crystallisation of their salicylates. The pyrrolidines of general formula I produced according to the invention form crystalline salts with organic and inorganic acids and in their production it is advantageous to start from carefully purified bases.

It is often advantageous to prepare the salts of weak acids by first converting the bases into salts of strong mineral acids and then transforming these into salts of weak acids.

The new pyrrolidine compounds according to the invention possess sympathomimetic properties, i.e. they are able to provoke adrenaline-like effects on the organs subordinate to the sympathetic nervous system. In practice, however, it is not always desirable that all these effects occur at the same time, and it is the object and aim of the organic chemist to produce synthetic substances which cause only some of these effects.

In the new pyrrolidine compounds, those compounds substituted in the phenyl nucleus with two hydroxyl groups, show a specific influence on the peripheral circulation, for example 3 - (*m,p* - dihydroxyphenyl) - 5-methyl - pyrrolidine, whilst the compounds substituted with one or three hydroxyl groups, improve predominantly the heart performance and only slightly influence the peripheral circulation, for example 3 - (*p* - hydroxyphenyl) - 5 - methyl - pyrrolidine, 3 - (*m*-hydroxyphenyl) - 5 - methyl - pyrrolidine, 3 - (*o,m,p* - trihydroxyphenyl) - 5 - methylpyrrolidine and 3 - (*o,m,p* - trimethoxyphenyl) - 5 - methylpyrrolidine. Moreover, some of the compounds, for example 3 - (*p*-hydroxyphenyl) - 5 - methylpyrrolidine have mucous membrane-contrasting activity, whereas a stimulating action is predominant in 3-(*m,p* - methylenedioxyphenyl) - 5 - methylpyrrolidine. In contrast to the known compound Aludrin, it is particularly surprising that the pyrrolidine compounds are extremely stable in the presence of more than one hydroxyl group, and thus appear particularly suitable for oral therapy.

Preferred compounds according to the invention include:—

3 - (*p* - Hydroxyphenyl) - 5 - methylpyrrolidine hydrochloride

3 - (*m* - Hydroxyphenyl) - 5 - methyl-pyrrolidine hydrochloride

3 - (*m,p* - Dihydroxyphenyl) - 5 - methyl-pyrrolidine hydrobromide

3 - (*m* - Hydroxyphenyl) - 2,5 - dimethyl-pyrrolidine hydrochloride

3 - (*p* - Hydroxyphenyl) - 2,5 - dimethyl-pyrrolidine hydrochloride

3 - (*p* - Hydroxyphenyl) - 2,2,5 - trimethyl - pyrrolidine hydrochloride

3 - (*m,p* - Methylenedioxyphenyl) - 3-methyl - pyrrolidine

3 - (*o,m,p* - Trihydroxyphenyl) - 5-methyl - pyrrolidine hydrochloride

3 - (*o,m,p* - Trimethoxyphenyl) - 5-methyl - pyrrolidine hydrochloride.

3 - (*p* - hydroxy - *m* - bromophenyl) - 5-methyl - pyrrolidine acetate.

The compounds of the invention may be formulated for administration in conjunction with a pharmaceutical carrier or excipient. The formulations may take the form of, for example, tablets, dragees, capsules, drops, syrups, linctuses, elixirs or suppositories. Unitary or dosage unit formulations are preferred, each dosage unit preferably containing 1—15 mg, advantageously 5—10 mg of a compound according to the invention. The carrier may comprise conventional pharmaceutical excipients, for example, starch, lactose, highly dispersed silica, polyvinyl pyrrolidone, glycerol, a buffer, e.g. borax/boric acid, water, alcohol, magnesium stearate or stearic acid, or flavouring, sweetening, dispersing or suspending agents.

In order that the invention may be well understood, the following examples are given by way of illustration only. The melting and boiling points in the examples are in °C.

EXAMPLE 1.

3-(*p*-Methoxyphenyl)-5-methyl-pyrrolidine

237.3 g. of 1 - nitro - 2 - (*p* - methoxyphenyl) - pentanone - (4) (m.pt.70—81°C.) are suspended in 1.5 litres of methanol and hydrogenated at 100—150 atm. hydrogen pressure and 70°C. in an autoclave in the presence of Raney nickel as catalyst. When the hydrogen absorption has been completed, the catalyst is filtered off, the solvent distilled off and the residue fractionally distilled *in vacuo*. Only one of the two theoretically possible stereoisomers is obtained.

Colourless oil of the boiling point 102°/1mm.

Yield 134—144 g. (70.2—75.4% of the theory).

For the preparation of the hydrochloride the base is suspended in 250 ml. of water and neutralised with 2 N HCl, which dissolves the base. The aqueous solution is carefully decolourised with active charcoal and then evaporated to dryness under water pump vacuum. The crystalline residue is recrystallised from acetonitrile - ethyl acetate or isopropanol. Melting point 154—168°C.

The following compounds were also produced by the above procedure:—

3 - (*m* - methoxyphenyl) - 5 - methyl-pyrrolidine. B.pt: 165—167°/14 mm.

3 - (*p* - methoxyphenyl) - 2 - ethyl - 5-methyl - pyrrolidine. B.pt: 165—168°/14 mm.

3 - (*m,p* - methylenedioxyphenyl) - 3-methyl - pyrrolidine. B.pt: 120—123°/0.05 mm.

3 - (*o,p* - dimethoxyphenyl) - 5 - methyl-pyrrolidine. B.pt: 118°/0.01 mm.

3 - (*o,o'*,*m* - trimethyl - *p* - methoxyphenyl) - 5 - methyl - pyrrolidine. B.pt: 132°/0.01 mm.

3 - (*m,p* - dimethoxyphenyl) - 5 - methyl-pyrrolidine. B.pt: 122°/0.1 mm.

3 - (*o,m* - dimethoxyphenyl) - 5 - methyl-pyrrolidine. B.pt: 120—121°/0.05 mm.

3 - (*m* - methyl - *p* - methoxyphenyl) - 5-methyl - pyrrolidine. B.pt: 122°/1 mm.

3 - (*p* - methoxyphenyl) - 5 - isobutyl-pyrrolidine. B.pt: 110—114°/0.01 mm. (produced from 1 - nitro - 2 - (*p* - methoxyphenyl) - 6 - methyl - heptanone - (4).).

3 - (*m,p* - dimethoxyphenyl) - 5 - isobutyl-pyrrolidine. B.pt: 125—130°/0.01 mm. (produced from 1 - nitro - 2 - (*m,p* - dimethoxyphenyl) - 6 - methyl - heptanone - (4).).

3 - (*o,m,p* - trimethoxyphenyl) - 5 - methyl-pyrrolidine. B.pt 124—126°/0.04 mm. (produced from 1 - nitro - 2 - (*o,m,p* - trimethoxyphenyl) - pentanone - (4).

3 - (*o,m,p* - trimethoxyphenyl) - 5 - methyl-pyrrolidine hydrochloride; m.pt 162°C.

3 - (*m,p* - methylenedioxy phenyl) - 3-methyl - pyrrolidine hydrochloride; m.pt 136—137°C.

EXAMPLE 2.

3-(*p*-Methoxyphenyl)-2-methyl-pyrrolidine

20.3 of β - (*p* - Methoxyphenyl) - laevulinic acid nitrile (m.pt. 101—102°) are dissolved in 150 ml. of warm abs. ethanol and hydrogenated in the presence of Raney nickel catalyst at 100°C. and 100 atm. hydrogen pressure in an autoclave. When the absorption of hydrogen is completed, the catalyst is filtered off, the solvent distilled off and the residue fractionally distilled *in vacuo*.

Colourless oil, b.pt. 74—75°C./0.005 mm. Yield 12.2 g.

Dibenzoyl tartrate m.pt. 154—155°C.

The following compounds were produced by the method described in Example 2.

3 - (*m,p* - dimethoxyphenyl) - 4 - phenyl-5 - methyl pyrrolidine. B.pt 163—168°/0.001 mm.

3 - (*p* - methoxyphenyl) - 4 - phenyl - 5-methyl - pyrrolidine. B.pt. 145—150°/0.001 mm.

EXAMPLE 3.

3-(*p*-hydroxyphenyl)-5-methyl-pyrrolidine

313.4 g. of 1 - nitro - 2 - (*p* - benzyloxyphenyl) - pentanone - (4) (m.pt 126°) are hydrogenated in 1.5 litres of methanol with Raney nickel as catalyst at 70°C. and 100—150 atm. hydrogen pressure in an autoclave. During hydrogenation ring closure and simultaneous splitting off of the benzyl group take place. When the absorption of hydrogen is completed, the catalyst is filtered off and the solution evaporated to dryness. The crystalline residue (containing resins) is treated with 1000 ml. of iron-free hydrochloric acid, which dissolves the 3 - (*p* - hydroxyphenyl)-5 - methyl - pyrrolidine. The resins are separated off and rejected. The aqueous solution is decolourised with iron-free active charcoal. The solution must be completely colourless. It is evaporated *in vacuo* to dryness, and the 3 - (*p* - hydroxyphenyl) - 5 - methyl-pyrrolidine hydrochloride crystallises out in almost pure state and is recrystallised once from acetonitrile.

Yield 59.0—64.5 g. (27.7—30.2% of the theory)

M.pt 216—219°.

Hydrobromide m.pt 192—194°.

The following compounds were prepared by the method described in Example 3.

3 - (*m* - hydroxyphenyl) - 5 - methyl-pyrrolidine hydrochloride. M.pt 130—131°C.

3 - (*p* - hydroxyphenyl) - 2,5 - dimethyl-pyrrolidine hydrochloride M.pt 183—187°C.

3 - (*m* - methyl - *p* - hydroxyphenyl) - 3-methyl - pyrrolidine. M.pt 179—180.5°C. (from acetonitrile).

3 - (*p* - hydroxyphenyl) - 2,2,5 - trimethyl - pyrrolidine hydrochloride. M.pt 270—272°C.

EXAMPLE 4.

3-(*p*-methoxyphenyl)-5-methyl-pyrrolidine

40 g. of 1 - nitro - 2 - (*p* - methoxyphenyl)-pentanone - (4) (m.pt 70—71°) are dissolved in 250 ml. of methanol and reduced on a lead cathode with addition of 50% sulphuric acid. The anode (in 50% sulphuric acid) is separated from the cathode compartment by a diaphragm. The current density should be at least 0.1 amp./cm². The current intensity is adjusted by addition of the corresponding quantity of 50% sulphuric acid. In the course of the electrolysis further sulphuric acid must be added in order to maintain the current density constant, and the substance must remain in solution during the whole course of the electrolysis. The temperature in the reaction vessel is maintained at 30—35°C. by cooling. The end of the reduction is easily recognised from increased evolution of hydrogen at the cathode. In general, the current consumption is slightly above the theoretical value. For purification, the red-brown coloured solution from the cathode compartment is diluted with approx. 300 ml. of water. A small quantity of a neutral substance separates out in the form of oily drops which are extracted with ether. The solution is made alkaline with excess caustic soda solution and the liberated base taken up in ether. After drying over potash it is fractionally distilled.

Main fraction: colourless oil.

Boiling point: 104—106°/2 mm.

Yield: 33—37% of the theory.

From 1 - nitro - 2 - (*m,p* - methylenedioxy - phenyl) - pentanone - (4), 3 - (*m,p*-methylenedioxy - phenyl) - 5 - methyl-pyrrolidine was produced by the method described in Example 4.

Colourless oil.

Boiling point 122°/0.05 mm.

Yield 51.5% of the theory.

EXAMPLE 5.

3-(*p*-Methoxyphenyl)-5-methyl-pyrrolidine

237.5 g. of 1 - nitro - 2 - (*p* - methoxyphenyl) - pentanone - (4) are dissolved in 1200 ml. of hot glacial acetic acid and in 500 g. of zinc dust are added in small portions with stirring at boiling point. When all the zinc dust has been added, the solution is boiled for 2 further hours under reflux, and poured into about 3 litres of water. Undissolved matter is filtered off, and the aqueous solution made alkaline with concentrated sodium hydroxide. The 3 - (*p* - methoxyphenyl) - 5 - methyl - pyrroline separates out as an oil. It is taken up in ether, the ethereal solution dried over potash, the solvent distilled off and the residue fractionally distilled *in vacuo*.

Boiling point 110°C./1 mm.

Yield 79.5—86 g. (42.45—5% of the theory).

The 3 - (*p* - methoxyphenyl) - 5 - methyl-pyrroline thus obtained is hydrogenated in 400 ml. of methanol with platinum oxide as catalyst in a pressure vessel at about 80° and 3—5 atm. hydrogen pressure and the product worked up.

Yield: 3 - (*p* - methoxyphenyl) - 5-methyl - pyrrolidine: 87—95% of the theory.

3 - (*m,p* - methylenedioxy - phenyl) - 5-methyl - pyrroline was produced from 1-nitro - 2 - (*m,p* - methylenedioxy - phenyl)-pentanone - (4) by reduction with zinc in glacial acetic acid as described above. B.pt 122°/1 mm. Reduction in methanol at 100° and 100 atm. hydrogen pressure with Raney nickel or Raney cobalt as catalyst yields 3-(*m,p* - methylenedioxy - phenyl) - 5 - methyl-pyrrolidine.

Colourless oil: b.pt 120—122°/0.05 mm.

If PtO_2 as hydrogenation catalyst is used, a hydrogen pressure of 3—4 atm. is sufficient for the hydrogenation in methanol at about 80°.

EXAMPLE 6.

3 - (*p* - hydroxyphenyl) - 4 - phenyl - 5-methyl - pyrrolidine

71 g. of α - (*p* - benzoyloxyphenyl) - β-phenyl - laevulinic acid nitrile are suspended in 700 ml. of ethanol and hydrogenated with Raney nickel at 70° and 100 atm. in an autoclave. Ring closure and simultaneous splitting off of the benzyl group is thus effected. After the hydrogenation the catalyst is filtered off and the solvent evaporated. The residue is taken up in iso-propanol and the solution neutralised with ethereal hydrochloric acid.

Hydrochloride: m.pt. 275°C. (dec.)

Acetate: m.pt 120—122°C.

EXAMPLE 7.

3 - (*p* - Methoxyphenyl) - 4 - (2,5 - endomethylene - cyclohexyl - (1)) - pyrrolidine

264.4 g. of crude α - (*p* - methoxyphenyl) α^1 - (2,5 - endomethylenecyclohexen - Δ^3 - yl-(1)) - succinic acid nitrile (produced from α-(*p* - methoxy - phenyl) - β - (2,5 - endomethylenecyclohexen - Δ^3 - yl) - (1)) - acrylonitrile by addition of HCN) are hydrogenated in 1500 ml. of methanol with Raney nickel as catalyst at 100° and 150 atm. hydrogen pressure in an autoclave. To isolate the product the catalyst is filtered off, the solvent distilled off and the residue taken up in 600 ml. of 2 N hydrochloric acid. The hydrochloric acid solution is twice extracted with ether and then made alkaline with sodium hydroxide solution to separate the base. The ethereal solution is dried over potash, the solvent distilled off and the residue fractionally distilled *in vacuo*.

B.pt 131—135°/0.01 mm. Yield 53% of the theory.

Hydrochloride m.pt 200°C. (from iso-propanol)

Acetate m.pt 105—108°C. (from ethyl acetate).

3 - (*n* - Butyl - (1)) - 3 - (*p* - methoxyphenyl) - pyrrolidine, B.pt 150—155°/0.05 mm was prepared from α - (*n* - butyl) - α-(*p* - methoxyphenyl) - succinic acid - dinitrile by the method described in Example 7.

EXAMPLE 8.

3-(*p*-Methoxyphenyl)-4-methyl-pyrrolidine

55 g. of 2 - methyl - 3 - cyano - 3-(*p* - methoxyphenyl) - propionaldehyde diethylacetal (b.pt 135—140°/0.01 mm) [produced from *p* - methoxybenzyl cyanide, sodamide and α - bromopropionaldehyde diethylacetal] are hydrogenated in 700 ml. of methanol with Raney nickel as catalyst at 100° and 80—100 atm. hydrogen pressure in an autoclave. The product is isolated as described previously. The base is obtained as mixture of two stereoisomeric forms. B.pt 158—62°/12 mm. Yield: 28.4 g. (74% of the theory).

The following compounds were obtained from the corresponding cyano - aldehyde acetals by the method described in Example 8.

3 - (*p* - methoxyphenyl) - pyrrolidine. B.pt 112—116°C./0.3 mm.

3 - (*p* - methoxyphenyl) - 4 - ethyl-pyrrolidine. B.pt 125—130°C./0.05 mm.

3 - (*p* - methoxyphenyl) - 4 - *n* - propyl-idine. B.pt 130—135°C./0.05 mm.

3 - (*n* - butyl - (2)) - 3 - (*p* - methoxy-phenyl) - pyrrolidine. B.pt 145—148°C./0.01 mm.

EXAMPLE 9.

3-(*p*-Methoxyphenyl)-pyrrolidine

A hot solution of 95.5 g. of (3 - (*p*-methoxyphenyl) - pyrrolidone - (5), m.pt 127—130 (from methanol) [prepared by catalytic reduction from β - cyano - β - (*p*-methoxyphenyl) - propionic acid ethyl ester, b.pt 128°/0.01 mm.] in 900 ml. of abs. tetrahydrofuran is added with stirring to 23 g. of lithium aluminium hydride in 150 ml. of tetrahydrofuran during 20 minutes, and the mixture boiled for 5 hours under reflux. The solvent is then distilled off on a boiling water bath. The residue is mixed with 300 ml. of ether and then decomposed first with 50 ml. of water and then with 200 ml. of concentrated hydrochloric acid. The ether layer is separated off and the aqueous phase re-extracted several times with ether. The aqueous solution is then made strongly alkaline with conc. sodium hydroxide solution and continuously extracted with ether for 4 hours. The ether extract is dried over potash, the solvent distilled off and the residue fractionally distilled *in vacuo*.

B.pt 157°/13 mm.

Yield 61.0 g = 69% of the theory.

Hydrochloride: M.pt 132—134° (from acetonitrile).

EXAMPLE 10.

3 - (*p* - hydroxy - *m* - bromo - phenyl)-5 - methyl - pyrrolidine

30 g. of pure 3 - (*p* - hydroxyphenyl) - 5-methyl - pyrrolidine hydrobromide are dissolved in 400 ml. of hot chloroform and a solution of 18.6 g. of bromine in 100 ml. of chloroform is added dropwise with stirring. The hydrogen bromide formed at the nitrogen atom is distilled off, and boiling under reflux is continued, until no more hydrogen bromide is evolved. On cooling, 3 - (*p* - hydroxy - *m*-bromophenyl) - 5 - methyl - pyrrolidine-hydrobromide crystallises out. It is recrystallised from a small quantity of water.

M.pt 178—179° (from water).

Yield: 76.5% of the theory.

The hydrobromide is difficulty soluble in water.

For the preparation of the acetate, the hydrobromide is dissolved hot in water and made weakly alkaline with ammonia. On cooling, the initially oily base crystallises out.

It is filtered with suction, thoroughly washed with a large volume of water and then dissolved in glacial acetic acid. The excess glacial acetic acid is distilled off and the residue recrystallised from a little alcohol.

M.pt of the acetate: 146—148° (from ethanol).

EXAMPLE 11.

3 - (*o,p* - Dimethoxy - bromophenyl) - 5-methyl - pyrrolidine

9.5 g. of 3 - (*o,p* - dimethoxy phenyl) - 5-methyl - pyrrolidine-base (B.pt 118°/0.01 mm) are dissolved in 50 ml. of glacial acetic acid and 3 ml. of bromine in 50 ml. acetic acid are added dropwise with stirring. Stirring is continued for one hour and the solvent is then distilled off *in vacuo*. The residue is triturated with acetic acid ester, to crystallise the 3 - (*o,p* - dimethoxy - bromo phenyl)-5 - methyl - pyrrolidine hydrobromide. The salt is recrystallised from acetonitrile.

Yield: 9.2 g. Paper-chromatographically uniform.

Melting Point 200—205°.

The position of the bromine atom in the phenyl group is not exactly known, but is either in the 3- or 5-position.

3 - (*o,o*^{1},*m* - trimethyl - *p* - methoxy - *m*^{1}-bromo - phenyl) - 5 - methylpyrrolidine, m.pt 197°C., was analogously obtained.

EXAMPLE 12.

3-(*p*-Methoxyphenyl)-pyrrolidine

44.0 g. of β - (*p* - methoxyphenyl) - γ-nitro - butyronitrile, [prepared from *p*-methoxycinnamic acid nitrile and nitromethane], are dissolved in 500 ml. of methanol and hydrogenated at 80° with Raney nickel as catalyst, at 100 atm. hydrogen pressure in an autoclave. The product is isolated as previously described.

B.pt 159—160°C./15 mm.

Yield: 21.2 g. = 59.5% of the theory.

Hydrochloride: m.pt 132—135° (from acetonitrile).

2 - methyl - 3 - (*p* - methoxyphenyl)-pyrrolidine B.pt 125—130C./0.05 mm. was analogously obtained from *p* - methoxycinnamic acid nitrile by reaction with nitroethane and subsequent hydrogenation.

EXAMPLE 13.

Ether-splitting

95.6 g. of 3 - (*p* - methoxyphenyl) - 5-methyl - pyrrolidine, produced according to Example 1, are heated for 4 hours in 150 ml. of hydrobromic acid (density ab. 1.45) on a water bath, and the solution evaporated to dryness at the water pump. 3-(*p*-hydroxyphenyl) - 5 - methyl - pyrrolidine hydrobromide is formed.

Yield: 89.5—95.0 g. (69.5—73.5% of the theory).

Melting point 192—194°C.

The following compounds were analogously produced: 3 - (*m,p* - dihydroxyphenyl) - 5-methyl - pyrrolidine hydrobromide. M.pt 183—195°C. (from ethanol); (starting from 3 - (*m,p* - dimethoxyphenyl) - 5 - methyl-pyrrolidine);

3 - (*m* - hydroxy - phenyl) - 5 - methyl-pyrrolidine hydrochloride M.pt 130—131°C. (from isopropanol/ethyl acetate) (starting from 3 - (*m* - methoxyphenyl) - 5 - methyl-pyrrolidine); using the method of preparation described in Example 13, the hydrobromide is first obtained. It is dissolved in water, the solution made weakly alkaline with ammonia and the free base taken up in ether. After evaporating off the ether, the base is converted into the hydrochloride with aqueous hydrochloric acid.

3 - (*p* - hydroxyphenyl) - 2 - ethyl - 5-methyl - pyrrolidine hydrochloride, m.pt 183—185° (from isopropanol/ethyl acetate) (starting from 3 - (*p* - methoxyphenyl) - 2-ethyl - 5 - methyl - pyrrolidine). The hydrochloride is prepared as described above.

3 - (*m* - methyl - *p* - hydroxyphenyl) - 5-methyl - pyrrolidine hydrochloride M.pt 178—180° (from isopropanol) (starting from 3 - (*m* - methyl - *p* - methoxyphenyl) - 5-methyl - pyrrolidine). The hydrobromide which is first obtained is converted into the free base with ammonia, and then into the hydrochloride.

3 - (*o,p* - dihydroxyphenyl) - 5 - methyl-pyrrolidine hydrobromide, M.pt 129—133°C. (from acetonitrile/isopropanol); (starting from 3 - (*o,p* - dimethoxyphenyl) - 5 - methyl-pyrrolidine).

3 - (*o,m* - dihydroxyphenyl) - 5 - methyl-pyrrolidine hydrobromide, m.pt 141—144°C. (from isopropanol/ethyl acetate), (starting from 3 - (*o,m* - dimethoxy - phenyl - 5-methyl - pyrrolidine).

3 - (*p* - hydroxyphenyl) - 4 - phenyl - 5-methyl - pyrrolidine acetate. M.pt 160—164°C. (from isopropanol); (starting from 3-(*p* - methoxy - phenyl) - 4 - phenyl - 5-methyl - pyrrolidine).

The hydrobromide first obtained is converted into the free base with ammonia, and then into the acetate.

3 - (*m,p* - dihydroxyphenyl) - 4 - phenyl-5 - methyl - pyrrolidine hydrobromide +1 mol water of crystallisation. M.pt 126—128°C. (from water) (starting from 3 - (*m,p*-dimethoxyphenyl) - 4 - phenyl - 5 - methyl-pyrrolidine).

3 - (*p* - hydroxyphenyl) - 5 - *iso* - butyl-pyrrolidine hydrochloride, m.pt 140—142°C. (from *iso*propanol/ethyl acetate) (produced from 3 - (*p* - methoxyphenyl) - 5 - *iso*-butyl - pyrrolidine).

[The hydrobromide which is first obtained is converted into the free base as previously described and then into the hydrochloride].

3 - (*m,p* - dihydroxyphenyl) - 5 - *iso*-

butyl - pyrolidine hydrobromide, m.pt 177—178°C. (isopropanol/ethyl acetate) produced from 3 - (*m,p* - dimethoxyphenyl) - 5 - *iso*-butyl - pyrrolidine.

3 - (*o,m,p* - trihydroxyphenyl) - 5 - methyl-pyrrolidine hydrochloride $+1/2\ H_2O$, m.pt 192—193° (from isopropanol) produced from 3 - (o,*m,p* - trimethoxyphenyl) - 5 - methyl-pyrrolidine hydrochloride (M.pt 162°).

The hydrobromide which is first obtained is recrystallised from alcohol/ethyl acetate, converted into the free base in the manner stated, and the hydrochloride produced in usual manner.

Example 14.

Separation of stereoisomers

230 g. of pure 2,5 - dimethyl - 3 - (*p*-methoxyphenyl) - pyrrolidine, produced by the method described in Example 1 from 2 - nitro-3 - (*p* - methoxy - phenyl) - hexanone - (5) are dissolved in 250 ml. of ethyl acetate. 154 g. of pure, crystallised salicyclic acid are added to this solution. A clear solution is formed on warming, from which a part of the base used crystallises out as the salicylate on standing.

(a) The salicylate which has crystallised out is separated from the mother liquor and recrystallised from ethyl acetate to constant melting point. M.pt 164° (salicylate of the α-form). Yield 24% based on the base used. The base can be liberated from the salicylate with aqueous sodium hydroxide solution. B.pt 90°C./0.01 mm. The base of the α-form thus obtained is gas-chromatographically uniform.

(b) The combined acetic ester mother liquors are evaporated to dryness. The base is liberated from the solid residue with aqueous sodium hydroxide and then distilled. B.pt 90—91°C./0.01 mm. This base is converted into the hydrochloride, which is recrystallised to constant melting point from acetone. M.pt of the hydrochloride of the β-form 132°C. The yield of hydrochloride amounts to 26% of the base originally used. The base can be obtained from the salt in the usual manner. B.pt 90°C./0.01 mm. Gas-chromatographically it is likewise uniform, but not identical with the α-form.

(c) The α-form of 2,5 - dimethyl - 3 - (*p*-hydroxyphenyl) - pyrrolidine can be produced from the base obtained according to (a) by the method described in Example 13 (ether-splitting).

Hydrochloride m.pt 223° (from isopropanol).

The β-form of 2,5 - dimethyl - 3 - (*p*-hydroxyphenyl) - pyrrolidine is produced from the hydrochloride obtained according to (b) analogously to Example 13.

Hydrochloride m.pt 199° (from isopropanol).

Example 15

(Process 8)

A hot solution of 102.5 g. of *p* - methoxyphenyl - succinimide in 800 ml. of absolute dioxan is slowly added to 45 g. lithium aluminium hydride in 250 ml. of absolute dioxan and the mixture heated for 4½ hours under reflux.

The product is isolated as described in Example 9. 64.5 g. (=72.5% of the theory) of 3 - (*p* - methoxyphenyl) - pyrrolidine, b.pt 156°C./12 mm are obtained.

M.pt of the acid oxalate 121—123°C.

Analogously, 3 - (*p* - methoxyphenyl) - 4-*n* - propyl - pyrrolidine was produced from α - (*p* - methoxyphenyl) - α¹ - *n* - propyl-succinimide. M.pt of the acid oxalate 124—126°C.

Example 16 — Nose Drops

100 ml. of nose drops contain:

3-(*p*-hydroxyphenyl)-5-methyl-pyrrolidine hydrochloride		0.200 g.
Methyl *p*-hydroxy-benzoate		0.020 g.
Propyl *p*-hydroxy-benzoate		0.010 g.
Boric acid		1.500 g.
Borax		0.075 g.
Demineralised water	to	100 mls.

EXAMPLE 17 — DROPS

100 ml. of drops contain:

3-(*m*-hydroxyphenyl)-5-methyl-pyrrolidine hydrochloride		0.750 g.
Methyl *p*-hydroxy-benzoate		0.070 g.
Propyl *p*-hydroxy-benzoate		0.030 g.
Alcohol		10.000 g.
Demineralised water	to	100 mls.

EXAMPLE 18 — TABLETS

Each tablet contains:

3-(*m*-hydroxyphenyl)-5-methyl-pyrrolidine hydrochloride	5.0 mg.
Lactose	32.5 mg.
Maize starch	42.0 mg.
Finely dispersed silicic acid	1.5 mg.
Soluble starch	3.0 mg.
Stearic acid	1.0 mg.
Tablet weight	85.0 mg.

EXAMPLE 19 — DROPS

100 mls. of drops contain:—

3-(*m,p*-dihydroxyphenyl)-5-methyl-pyrrolidine hydrochloride		0.75 g.
Methyl *p*-hydroxy-benzoate		0.07 g.
Propyl *p*-hydroxy-benzoate		0.03 g.
Tartaric acid		0.10 g.
Demineralised water	to	100 mls.

EXAMPLE 20 — TABLETS

Each tablet contains:—

3-(*m,p*-dihydroxyphenyl)-5-methyl-pyrrolidine hydrochloride	5.0 mg.
Lactose	45.0 mg.
Maize starch	39.0 mg.
Finely dispersed silicic acid	2.0 mg.
Soluble starch	3.0 mg.
Stearic acid	1.0 mg.
Tablet weight	95.0 mg.

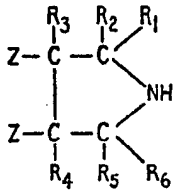
EXAMPLE 21 — AMPOULES

Each ampoule contains:—

3-(*m,p*-dihydroxyphenyl)-5-methyl-pyrrolidine hydrobromide		10 mg.
Sodium chloride		6 mg.
Double-distilled water	to	1.0 ml.

WHAT WE CLAIM IS:—

1. Phenyl pyrrolidines of the general formula



I

wherein R_1, R_2, R_3, R_4, R_5 and R_6, which may be the same or different, are hydrogen atoms or alkyl groups containing 1 to 6 carbon atoms, at least one of R_1, R_2, R_3 and R_6 representing a hydrogen atom and the symbols Z, which may have the same or different meanings represent hydrogen atoms or phenyl or endomethylenecycloalkyl groups, if desired substituted with one or more halogen atoms or alkyl, alkoxy, hydroxy or methylenedioxy groups, at least one of the symbols Z representing a phenyl group substituted with at least one alkoxy, hydroxy or methylenedioxy group, and their acid addition salts.

2. 3 - (*p* - Hydroxyphenyl) - 5 - methyl-pyrrolidine hydrochloride.

3. 3 - (*m* - Hydroxyphenyl) - 5 - methyl-pyrrolidine hydrochloride.

4. 3 - (*m,p* - Dihydroxyphenyl) - 5-methyl - pyrrolidine hydrobromide.

5. 3 - (*m* - Hydroxyphenyl) - 2,5 - dimethyl - pyrrolidine hydrochloride.

6. 3 - (*p* - Hydroxyphenyl) - 2,5 - dimethyl - pyrrolidine hydrochloride.

7. 3 - (*p* - Hydroxyphenyl) - 2,2,5 - trimethyl - pyrrolidine hydrochloride.

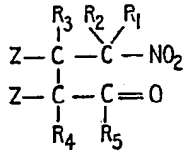
8. 3 - (*m,p* - Methylenedioxyphenyl) - 3-methyl - pyrrolidine.

9. 3 - (*o,m,p* - Trihydroxyphenyl) - 5-methyl - pyrrolidine hydrochloride.

10. 3 - (*o,m,p* - Trimethoxyphenyl) - 5-methyl - pyrrolidine hydrochloride.

11. 3 - (*p* - Hydroxy - m - bromophenyl)-5 - methyl - pyrrolidine acetate.

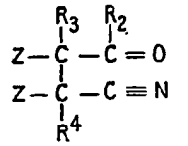
12. A process for the preparation of compounds as claimed in claim 1 in which R_6 is hydrogen, in which a compound of the general formula



II

where R_1, R_2, R_3, R_4, R_5 and Z have the meanings given in claim 1 is reduced and allowed to cyclise.

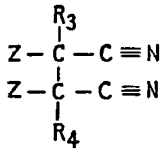
13. A process for the preparation of compounds as claimed in claim 1 in which R_1, R_5 and R_6 are hydrogen, in which a compound of the general formula



III

wherein R_2, R_3, R_4 and Z have the meanings given in claim 1, is reduced and allowed to cyclise.

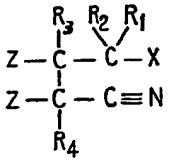
14. A process for the preparation of compounds as claimed in claim 1 in which R_1, R_2, R_5 and R_6 are hydrogen, in which a compound of the general formula



IV

where R_3, R_4 and Z have the meanings given in claim 1, is reduced and allowed to cyclise.

15. A process for the preparation of compounds as claimed in claim 1 in which R_5 and R_6 are hydrogen in which a compound of the general formula



V

where R_1, R_2, R_3, R_4 and Z have the meanings given in claim 1 and X is an amino or nitro group is reduced and allowed to cyclise.

16. A process as claimed in any of claims 12 to 15 in which the reduction is effected by reaction with hydrogen in the presence of a hydrogenation catalyst.

17. A process as claimed in claim 16 in which the reduction is effected at 50 to 150°C.

18. A process as claimed in claim 17 in which the reduction is effected at 80 to 100°C.

19. A process as claimed in any of claims 16 to 18 in which the catalyst is a Raney metal and the reaction pressure is 80—150 atmospheres excess pressure.

20. A process as claimed in any of claims 16 to 18 in which the catalyst is a noble metal or rhodium and the reaction pressure is 5—20 atmospheres excess pressure.

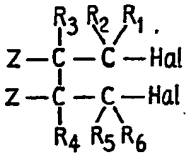
21. A process as claimed in any of claims 16 to 20 in which the reaction is carried out in an alcohol or ether as solvent.

22. A process as claimed in claim 21 in which the ratio of solvent to starting material is about 5 : 1 (parts by volume).

23. A process as claimed in any of claims 12 to 15 in which the reduction is effected electrolytically.

24. A process as claimed in claim 23 in which the electrolysis is effected in 50% sulphuric acid.

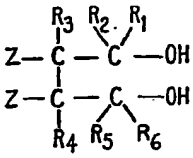
25. A process for the preparation of compounds as claimed in claim 1 in which a compound of the general formula



VI

wherein R_1, R_2, R_3, R_4, R_5, R_6 and Z have the meanings given in claim 1 and Hal is a chlorine, bromine or iodine atom, is reacted with ammonia or benzylamine, the N - benzyl group, where present, being subsequently removed.

26. A process for the preparation of compounds as claimed in claim 1 in which a compound of the general formula



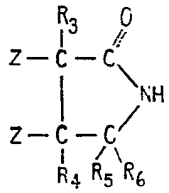
VII

in which R_1, R_2, R_3, R_4, R_5, R_6 and Z have the meanings given in claim 1, or a diester thereof is reacted with ammonia or benzyl-

amine, the N - benzyl group, where present, being subsequently removed.

27. A process as claimed in claim 25 or claim 26 in which the reaction is effected in solution in an alcohol, an ether, or a hydrocarbon solvent.

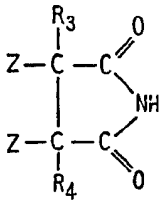
28. A process for the preparation of compounds as claimed in claim 1 in which R_1 and R_2 are hydrogen in which a compound of the general formula



VIII

in which R_3, R_4, R_5, R_6 and Z have the meanings given in claim 1 is reduced.

29. A process for the preparation of compounds as claimed in claim 1 in which R_1, R_2, R_5 and R_6 are hydrogen in which a compound of the general formula



IX

where Z, R_3 and R_4 have the meanings stated in claim 1 is reduced.

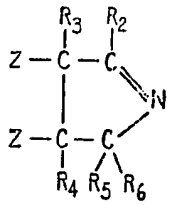
30. A process as claimed in claim 28 or claim 29 in which the reduction is effected with a metal hydride reducing agent.

31. A process as claimed in claim 28 or claim 29 in which the reduction is effected electrolytically.

32. A process as claimed in claim 28 or claim 29 in which the reduction is effected with hydrogen in the presence of an Adkin's catalyst.

33. A process as claimed in claim 32 in which the reduction is effected at 200—250 atmospheres excess pressure and at a temperature above 150°C.

34. A process for the production of compounds as claimed in claim 1 in which R_1 is hydrogen in which a pyrroline of the general formula



X

in which R_2, R_3, R_4, R_5, R_6 and Z have the meanings given in claim 1, is reduced catalytically.

35. A process for the preparation of compounds as claimed in claim 1 in which one or more of the phenyl groups carries a halogen atom, in which a compound as claimed in claim 1 is halogenated to introduce a halogen atom into a phenyl nucleus thereof.

36. A process for the preparation of compounds as claimed in claim 1 containing a phenyl group substituted with one or more hydroxy groups in which a compound as claimed in claim 1 containing a phenyl group substituted with one or more alkoxy groups is reacted with an ether-splitting agent to convert said alkoxy group(s) to hydroxy group(s).

37. A process as claimed in claim 36 in which said ether-splitting agent is hydrogen bromide.

38. A process as claimed in any one of claims 12 to 37 in which the stereoisomers of the compound as claimed in claim 1 are separated.

39. A process as claimed in claim 38 in which the separation of the stereoisomers is effected by fractional crystallisation of the salicylates of the bases claimed in claim 1.

40. A process as claimed in any of claims 12 to 39 substantially as herein described.

41. A process as claimed in any of claims 12 to 39 substantially as herein described with reference to any of Examples 1 to 15.

42. Pharmaceutical compositions containing a compound as claimed in claim 1 in conjunction with a pharmaceutical carrier or excipient.

43. Compositions as claimed in claim 42 in the form of tablets, dragees, capsules, drops, syrups, linctuses, elixirs or suppositories.

44. Compositions as claimed in claim 42 in dosage unit forms.

45. Compositions as claimed in claim 44 in which each dosage unit contains 1—15 mg. of a compound as claimed in claim 1.

46. Compositions as claimed in claim 45

in which each dosage unit contains 5 to 10 mg. of a compound as claimed in claim 1.

47. Compositions as claimed in any of claims 42 to 46 in which the carrier comprises starch, lactose, highly dispersed silica, polyvinylpyrrolidone, glycerol, a buffer, magnesium stearate, stearic acid, water, alcohol or flavouring, sweetening, dispersing or suspending agents.

48. Compositions as claimed in claim 42 substantially as herein described with reference to any of Examples 16 to 21.

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